IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

MERCK SHARP & DOHME PHARMACEUTICALS, SRL, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD. Defendants.	C.A. No. 07-1596 (GEB) (JJH) **REDACTED**

TEVA'S PROPOSED STATEMENT OF FACT

TABLE OF CONTENTS

Based upon the facts as presented at trial, this Court should hold that U.S. Patent No. 5,565,473 ("the '473 patent") is unenforceable and claims 18-22 of the patent are obvious over a combination of Young, Robert N., *Structural Analysis of Sulfido-Peptide Leuktorienes: Application to the Design of Potent and Specific Antagonists of Leukotriene D_4,* Advances in Prostaglandin, Thromboxane, and Leukotriene Research, vol. 19, pp. 643-646 (1989) ("Young 89"), U.S. Patent No. 5,104,882 ("the '882 patent") and EP 0 318 093 ("EP '093"). Judgment should be entered in favor of the Defendants.

I. Merck Withheld the Young 89 Reference during the Prosecution of the '473 Patent with an Intent to Mislead the PTO.

Before filing the priority application that eventually matured into the '473 patent, Dr. Young, the head of Merck's LTD_4 antagonist program, published a paper disclosing a model of the LTD_4 receptor and identifying the critical structural attributes for a potent LTD_4 antagonist. Young 89 was highly material to the prosecution of the '473 patent; it was relevant to the very point of novelty alleged by Merck and raised by the Examiner in three separate rejections during the prosecution of the '473 patent. Now, Merck asks this Court to infer that the patent prosecutor, Mr. Lopez, simply overlooked or did not recall the paper at the time of the prosecution. Merck has offered no contemporaneous evidence to support this implausible and unreasonable inference, or any other innocent explanation for the failure to disclose Merck's own work to the examiner. To the contrary, the

evidence presented at trial requires that this Court find that, during the prosecution, Mr. Lopez *was* aware of the Young 89 paper, and the model it disclosed, and that this highly material information was withheld from the U.S. Patent & Trademark Office ("PTO") with an intent to mislead.

A. *Young 89 Was Highly Material In the Context of the Patent Prosecution.*

1. The Context of the Prosecution History of the '473 Patent.

The evidence at trial established that Young 89 was highly material in the context of the prosecution that eventually resulted in the issuance of the '473 patent. A central issue during the prosecution of the '473 patent was the alleged non-obviousness of a secondary or tertiary alcohol over a primary alcohol at the "Q^2 position" of the compounds disclosed and claimed in the prior art. This was an issue that Merck placed front and center and was one that bedeviled the Examiner on no less than three occasions. It was with respect to this very issue – the obviousness of a secondary and tertiary alcohol at the Q^2 position – that Young 89 and its receptor model were directly relevant and highly material.

In a paper dated June 18, 1991, Merck identified the issue of the Q^2 position and the alleged non-obviousness of a secondary or tertiary alcohol at this position over the structurally similar prior art compounds. In that paper, Merck (through

prosecuting attorney Gabriel Lopez[1]) cited a prior art European patent application owned by Merck, EP '093 and argued that "[t]he present[ly] [claimed] compounds differ from EP 318,093 in that Q^2 is a secondary or tertiary alcohol or amine." Stipulated Fact, at p. 10, ¶ 73.[2] After considering Merck's representation, the Examiner rejected the application on this basis. In office actions dated October 8, 1991 and April 9, 1992, the Examiner rejected the pending claims on the basis that it would have been obvious to substitute a secondary or tertiary alcohol for a primary alcohol at the Q^2 position in the compounds disclosed in EP '093. *See id.* at pp. 10-11, ¶¶ 74, 81. Merck did not respond to either of these rejections, but instead abandoned the applications. *Id.* at pp. 10-11, ¶¶ 75-76, 82-83.

On May 26, 1992, the Examiner again rejected all pending claims in a subsequent continuation-in-part application on the basis that it would have been obvious to put a secondary or tertiary alcohol at the Q^2 position. However, rather than relying on EP '093, the Examiner turned to another Merck patent, U.S. Patent No. 4,851,409 ("the '409 patent"). As the Examiner correctly noted, the only difference between the claimed compounds and those disclosed in the '409 patent was the claimed secondary or tertiary alcohol at the Q^2 position. *See* Tr. 112:19-

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[1] Mr. Gabriel Lopez was Merck's in-house patent attorney with responsibility for prosecuting all of Merck's leukotriene antagonist patents. Tr. 7:11-23, 8:2-7, Lopez, Feb. 24, 2009, A.M. session.

[2] Stipulated Fact, at p. __, ¶ __ refers to the Stipulation of Facts section in the Revised Final Pre-Trial Order, submitted Jan. 28, 2009, at p. __, ¶ __.

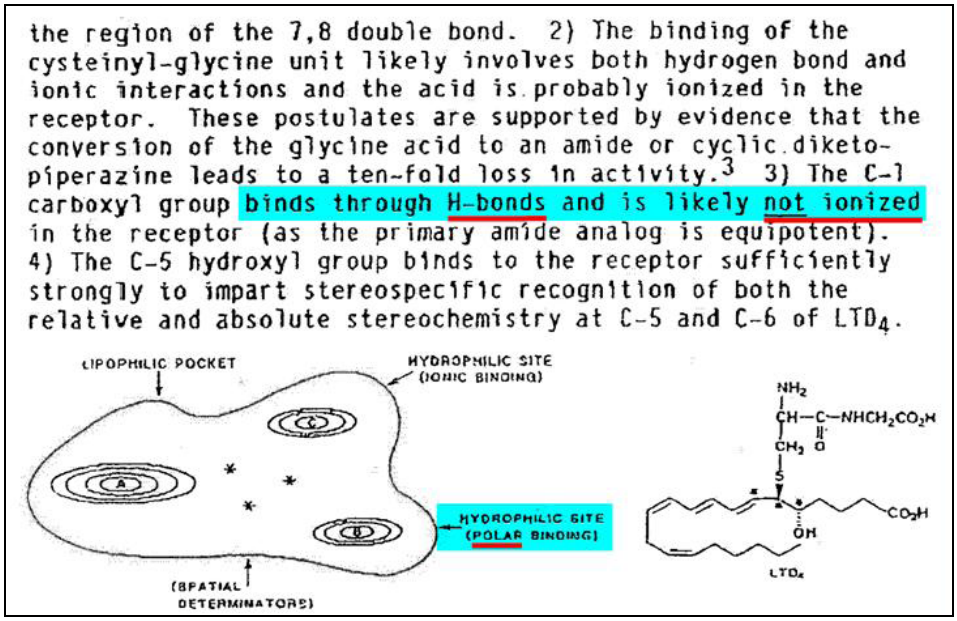
113:22, Lenz, Feb. 24, 2009, A.M. session. Thus, both Merck (through attorney Lopez) and the Examiner focused the prosecution on this single distinction between primary versus secondary/tertiary alcohols. DTX-1444, at 1444.605-606. At that time, no narrow claim specific to montelukast was pending; rather, the only pending claims were directed to a broad genus, or group, of compounds. *See* Tr. 110:19-111:17, Lenz, Feb. 24, 2009, A.M. session; DTX-1444, at 1444.0155-168.

Merck (again, through attorney Lopez) finally substantively responded to this third rejection on the primary alcohol prior art on August 26, 1992. *See* DTX-1444, at 1444.607-09. In the response, Lopez argued that the secondary or tertiary alcohol claimed in the pending claims was not obvious over the primary alcohol disclosed in the prior art. DTX-1444, at 1444.609; Tr. 54:2-7, Lopez, Feb. 24, 2009, A.M. session. The Examiner accepted Lopez's argument – in the next office action, no obviousness rejection was raised. *See* DTX-1444, at 1444.690-92. Lopez was thus able to obtain the '473 patent because he convinced the Examiner that a secondary or tertiary alcohol was not an obvious substitution for a primary alcohol in the Q^2 position of the structurally similar prior art LTD_4 antagonists disclosed in Merck's '409 patent.

2. The Disclosure of Young 89 – The Young Model.

The Examiner, however, was unaware of a critical Merck publication that supported his initial conclusion that a secondary or tertiary alcohol was an obvious

substitution for the prior art primary alcohol. Dr. Young, the head of Merck's leukotriene antagonist program, had previously developed and published a model, exemplified in Young 89. PTX-3283. The model was based on both a synthesis of publically available data, as well as Merck's internal activity data from its development program. Tr. 94:16-95:13, Young, Feb. 23, 2009, A.M. session. The model identified three parts of a leukotriene antagonist. In one position, which the model indicated would bond to pocket "B" of the receptor (as shown below), the model identified three attributes that were necessary for the group at that position in an antagonist – it had to be (1) polar; (2) not ionized; and (3) a hydrogen bond acceptor. Tr. 119:23-120:2; 121:16-122:4, Lenz, Feb. 24, 2009, A.M. session; PTX-3283, at 3283.0002; Tr. 98:10-99:19, Young, Feb. 23, 2009, A.M. session.



PTX-3283, at 3283.0002 (emphasis added)

This "B" pocket corresponded to the Q^2 side chain in the compounds of the '473 patent. Tr. 119:23-120:2, Lenz, Feb. 24, 2009, A.M. session.

Beyond disclosing the model, the Young 89 paper also disclosed that the model was used to develop one of Merck's most potent LTD_4 antagonists, L-660,711. As the paper explains, "The ultimate utility of this receptor model has been its application in the development of L-660,711, one of the most potent LTD_4 antagonist known." PTX-3283, at 3283.0003. The article continues by reporting that L-660,711 has a potency of 0.9 nM; as explained at trial, this "nanomolar" potency indicated that this compound was extremely potent. Tr. 92:2-21, Lenz, Feb. 24, 2009, A.M. session. Neither the Young 89 paper, nor the model it disclosed, were ever submitted to the PTO during the prosecution that resulted in the '473 patent. Stipulated Fact, at p. 14, ¶ 121; DTX-1444 (prosecution history, showing that Young 89 was never submitted).

3. The Young Model, Disclosed in Young 89, was Highly Material.

The model disclosed in Young 89 presented a comprehensive synthesis of activity data that was a useful "executive summary" of more than 10 years of research on leukotriene antagonists. Tr. 117:16-118:2, Lenz, Feb. 24, 2009, A.M. session. Moreover, although Merck did disclose to the PTO prior art patents that identified the structures of numerous LTD_4 antagonists, *see* Tr. 62:23-63:21, Lopez, Feb. 24, 2009, A.M. session, the article presented at least two additional

pieces of information that were not disclosed to the PTO in any form. First, the model presented important activity data, both the explicit data directed to L-660,711 and additional compounds, and also other activity data upon which the model was based. Tr. 94:16-25; 95:9-18, Young, Feb. 23, 2009, A.M. session; Tr. 118:3-6, Lenz, Feb. 24, 2009, A.M. session. Second, the model as disclosed in Young 89 indicated that an antagonist needed not only to hydrogen bond, but to also be a hydrogen bond *acceptor* to bond at the B-pocket of the model. Tr. 117:16-18, 118:7-15, Lenz, Feb 24, 2009, A.M. session; Tr. 72:11-13, Gleason, Feb. 25, 2009, A.M. session; *Cf.* Tr. 76:20-77:19; 106:7-14, Young, Feb. 23, 2009, A.M. session. The fact that the group at this position needed to be a hydrogen bond acceptor (as opposed to a donor) was a new and important disclosure on what group could be placed at that location and still expect activity as an LTD_4 antagonist. None of the other prior art references disclosed by Merck to the PTO, including the '882, EP '093, the '409 and EP 0 399 818, contained any activity data for the compounds that were disclosed. Tr. 4:13-5:20, Gleason, Feb. 25, 2009, P.M. session.

The Young 89 paper, and the Young model it disclosed, would have been important to a reasonable examiner because it would have supported the prior rejection that the secondary or tertiary alcohol were obvious substitutions for the primary alcohol at the Q^2 position in the structurally similar prior art. The Young

model required a substituent that was polar, not ionized, and a hydrogen bond acceptor at the Q^2 position. Tr. 119:23:120:2, Lenz, Feb. 24, 2009, A.M. session; Tr. 98:10-99:19, Young, Feb. 23, 2009, A.M. session. The primary alcohol of the prior art '409 patent, upon which the examiner relied, would have been known to be polar, not ionized, and a hydrogen bond acceptor. Tr. 120:12-14, Lenz, Feb. 24, 2009, A.M. session; Tr. 13:14-18, Gleason, Feb. 25, 2009, P.M. session. The secondary and tertiary alcohols share these physicochemical attributes with a primary alcohol – they are also polar, not ionized, and hydrogen bond acceptors. Tr. 120:15-20, Lenz, Feb. 24, 2009, A.M. session; Tr. 13:19-14:3, Gleason, Feb. 25, 2009, P.M. session.[3] Thus, had the Examiner had the Young 89 reference, his initial rejection would have been reinforced. Tr. 122:5-17, Lenz, Feb. 24, 2009, A.M. session. Instead, without this reference, the examiner abandoned his obviousness rejection, and the '473 patent eventually issued.

Although Merck's expert witnesses at trial attempted to portray this model as being basically use, *see, e.g.*, Tr. 65:3-19, Gleason, Feb. 25, 2009, A.M. session; Tr. 25:21-26:5, Jorgensen, Feb. 26, 2009, A.M. session, the contemporaneous conduct, statements and actions demonstrate the importance of the model. For example, Dr. Young explained that his presentation of the model in Taiwan, related

[3] For this reason, Dr. Labelle testified that Merck turned to the tertiary alcohol shortly after the primary alcohol. Tr. 65:10-66:1, Labelle, Feb. 23, 2009, P.M. session.

to the Young 89 reference, was because Merck "wanted to show the world that [they] were major players in the [leukotriene] effort. And . . . being scientists, [they] ha[d] a degree of desire to be known in [their] own right. . . ." Tr. 105:1-106:6, Young, Feb. 23, 2009, A.M. session. In that reference, along with others, Merck repeatedly stressed the value and importance of the model.

- "Evaluating these data, we have been able to derive a model of the LTD_4 receptor which has allowed the rational analysis of interactions of known antagonists with the receptor and thus predict structural modifications which would improve potency." PTX-3283, at 3283.0001-0002.
- "Based on a growing body of knowledge on structure activity relationships and physical studies of sulfide-peptide leukotrienes, their analogs and on specific antagonists, a model of the LTD_4 receptor has been evolved which has proved useful in designing novel and potent LTD_4 receptor antagonists." PTX-3283, at 3283.0004.
- "In spite of the simplicity, this receptor model has proved very useful in the design and discovery of MK-571 [L-660,711], one of the most potent LTD_4 antagonists known to date." DTX-1256, at 304.

Merck's conduct in the 1988-91 timeframe also belies the current claim that the model was useless. Not only did Merck present the model externally, Dr. Young presented the model to Merck's own development team. Leger Dep. 130:4-20, May 14, 2008; Xiang Dep. 54:4-5, 55:1-57:20, July 17, 2008; Belley Dep. 26:3-6, 30:23-33:6, July 22, 2008. And Merck used the model to develop leukotriene antagonists. Dr. Young confirmed that his LTD_4 model "was one of the elements [Merck] used to try and select directions of research in terms of compound selection and synthesis." Tr. 108:10-13, Young, Feb. 23, 2009, A.M.

session. And Dr. Young's papers confirmed that the model was used to develop, among other compounds, L-660,711. PTX-3283.

In fact, the inventors acknowledged that the model played an important role in the decision to modify prior compounds and place a tertiary alcohol in the Q^2 position (the very question upon which the examiner focused) in the compound that became montelukast. Inventor Belley was the first Merck employee to synthesize a compound with a tertiary alcohol in that position. Belley Dep. 83:1-9, July 22, 2008. In deposition, Belley explained that this idea was "prompted" by a meeting in which Dr. Young presented his model. Belley Dep. 34:16-35:13, July 22, 2008.[4] Similarly, Inventor Labelle explained that from his perspective, "the tertiary alcohol was a likely modification." Tr. 60:6-10, Labelle, Feb. 23, 2009, P.M. session. Dr. Labelle further explained that it was the polar nature of the tertiary alcohol, consistent with the requirements of the Young model, which led him to believe it was a likely modification to obtain a leukotriene antagonist. Tr. 62:24-63:10, Labelle, Feb. 23, 2009, P.M. session. And Inventor Xiang explained that he believed Merck developed the model because it would be useful in designing LTD_4 antagonists. Xiang Dep. 62:14-63:6, July 17, 2008.

Even Merck's expert, Dr. Gleason, acknowledged the importance of the Young 89 paper, and the Young model, before trial. During trial, a paper co-

[4] Although Mr. Belley is still employed by Merck, he was not brought to trial and hence his testimony is from his deposition in this case.

authored by Dr. Gleason and other Smith Kline & French employees, including Kingsbury, was repeatedly discussed. *See* PTX-3131. Dr. Gleason explained that this chapter in Comprehensive Medicinal Chemistry was intended to cover the history of leukotriene antagonist research, including everything that was "scientifically sound." Tr. 57:12-58:2, Gleason, Feb. 25, 2009, A.M. session. After reviewing the history of leukotriene antagonist research for 15 pages, Dr. Gleason's article then turns to "Future Design of Specific LTD_4 Receptor Antagonists." PTX-3131, at 3131.0019. Gleason's article cites only one article in this forward-looking section, which it describes as disclosing "a model involving the analysis of the interaction of known antagonists with the receptor . . . (Figure 3) [fn 83]." PTX-3131, at 3131.0019. That article, identified in footnote 83, is the Young 89 paper. Tr. 33:11-17, Lenz, Feb. 25, 2009, A.M. session. Contrary to Merck's theory at trial, Dr. Gleason's article specifically notes that, "[t]he utility of this model is illustrated in the development of L-660,711." PTX-3131, at 3131.00021.

Dr. Gleason attempted to explain away the inconsistency between Merck's trial theory and his article by explaining that the Young 89 paper was merely cited as "an example of how" a medicinal chemist would go "down th[e] rational design approach." Tr. 83:23-84:7, Gleason, Feb. 25, 2009, A.M. session. But the article makes no suggestion that Young 89 is merely one example of a rational design

approach; Young 89 is the only article cited in the "Future Design" section of the chapter. Moreover, even if Young 89 were merely one of multiple references that helped a person of skill "to try to understand how LTD_4 and the antagonist interact with the receptor," it would be important to a reasonable examiner because, as Dr. Gleason himself explained, "the more you could understand [the interaction] at a molecular level, the more you might be able to move away from the known classes and start to design new types of compounds," *id.* at 83:11-16. Dr. Gleason thus acknowledged that his own contemporaneous article suggests that the Young model discloses important information concerning the development of a leukotriene antagonist. As such, the reference was highly material to the prosecution of the '473 patent.

During trial, Merck's witnesses identified a number of supposed weaknesses in the model disclosed in Young 89. For example, Dr. Young testified about the size of various substituents and the degree of polarity. Tr. 78:9-15; 80:11-21, Young, Feb. 23, 2009, A.M. session. And Dr. Gleason complained that the Young model makes no mention of the directionality of hydrogen bonding. Tr. 73:7-25, Gleason, Feb. 25, 2009, A.M. session. But these distinctions are beside the point for materiality. Here, the Examiner was specifically focused on the distinction between the primary alcohol (in the prior art) and the secondary or tertiary alcohol (in the pending broad claims). The Young model, as disclosed in Young 89,

specifically disclosed that the substituent in the Q^2 position needed to be polar, not ionized, and a hydrogen bond acceptor. All witnesses acknowledged that the primary, secondary and tertiary alcohols each meet these three critical requirements identified by the model. That there may be other distinctions between the primary, secondary and tertiary alcohols, not identified as important by the model, *see* Tr. 122:18-123:12, Lenz, Feb. 24, 2009, A.M. session, does not reduce (and certainly does not eliminate) the materiality of the model. As Dr. Lenz explained, Young 89 would have been important to a reasonable examiner in the context of the prosecution because "it would reinforce his initial rejection based on the primary alcohol being equivalent to the secondary and tertiary alcohols because it would have given him knowledge that what you needed there was something that was polar, non-ionized and hydrogen bonding which . . . all three alcohols are." Tr. 122:11-17, Lenz, Feb. 24, 2009, A.M. session.

B. *Young 89 Was Also Highly Material Because It Supported a Prima Facie Obviousness Rejection.*

The Young 89 paper was highly material for an additional reason – it would have, by itself or in combination with the '882 or '409 patent, supported a *prima facie* obviousness rejection. As discussed above, the Examiner correctly identified that the only distinction between the prior art and the broad claims (both pending and issued) was the tertiary alcohol at the Q^2 position of the pending claims. For example, Examples 27 and 28 of the '409 patent (which disclose L-660,711) only

differ from Example 18 of the '473 patent, which is specifically covered by claim 7, by the Q^2 position. L-660,711 has a dimethyl amide, while Example 18 of the '473 patent has a tertiary alcohol. Similarly, Example 97 of the '882 patent differs from example 5 of the '473 patent by only the same substitution. *See* Demonstrative Slide 32, Tr. 123:17-124:13, Lenz, Feb. 24, 2009, A.M. session. As the Young model taught a person of ordinary skill in the art that the dimethyl amide could be replaced by a tertiary alcohol, Young 89 renders at least the broad claims of the '473 patent *prima facie* obvious.

As explained in detail above, the Young model, as disclosed in Young 89, identifies three critical attributes at the Q^2 position of a leukotriene antagonist – it must be polar, non-ionized, and a hydrogen bond acceptor. Both the dimethyl amides of the prior art compounds, and the tertiary alcohol meet each of these three criteria. Tr. 124:7-13, Lenz, Feb. 24, 2009, A.M. session. The Young 89 paper thus renders the claims *prima facie* obvious. Tr. 124:18-125:17, Lenz, Feb. 24, 2009, A.M. session.

At trial, Merck argued that many different substituents would meet the three requirements of the Young model at the Q^2 position. As Dr. Lenz acknowledged, the tertiary alcohol is not the only group that meets the requirements of the Young model. "There are a variety of substitu[e]nts you can put in there that will have those properties, but there are not a large number of them. So, maybe there's a

dozen of them, roughly. Those are the ones you could put in there." Tr. 131:17-21, Lenz, Feb 24, 2009, A.M. session. *See also* Tr. 57:9-62:25, Lenz, Feb. 24, 2009, P.M. session. But Dr. Lenz also explained that a medicinal chemist would use various tools to create a hierarchy of compatible substituents. For example, a medicinal chemist would consider absorption, distribution, metabolism and excretion ("ADME"). Tr. 95:13-96:9, Lenz, Feb. 24, 2009, A.M. session. A medicinal chemist would also consider what had previously been disclosed in other patents, in order to develop a novel molecule that was not owned by a third party. Tr. 96:21-97:5, Lenz, Feb. 24, 2009, A.M. session. Finally, a medicinal chemist would keep the molecule as simple as possible. "And I guess the other thing, too, is simplicity. You want to keep the molecules relatively similar so you don't start introducing large amounts of different types of substituents because when you do that, you're likely to have them or possibly have them hit other receptors. . . . And that's not what you want." Tr. 97:6-11, Lenz, Feb. 24, 2009, A.M. session. Dr. Lenz thus explained that, applying these standard medicinal chemist tools, a tertiary alcohol would be at, or near, the top of the list of substituents to use at the Q^2 position even though other groups fit the Young model. Tr. 131:22-132:14, Lenz, Feb. 24, 2009, A.M. session. This is confirmed by the actual conduct of Inventor Belley, who was prompted to use an alcohol by Dr. Young's presentation of his model; the first compound Belley tested after hearing the presentation on the

model had a tertiary alcohol. Belley Dep. 26:11-16, 30:23-32:17, 34:16-35:13, 115:16-21, July 22, 2008.

Dr. Gleason did not testify to the contrary. Rather, all Dr. Gleason stated was that multiple substituents fit the Young model at the Q^2 position, a fact Dr. Lenz readily acknowledged. *See*, *e.g.*, Tr. 71:5-7, Gleason, Feb. 25, 2009, A.M. session; *id.* at 74:18-19. But Dr. Gleason never identified any hierarchy of substituents – he never explained why or if a medicinal chemist of ordinary skill would try any substituent before (or after) any other.[5] As Dr. Lenz explained, however, based on Young 89 and common tools used by medicinal chemists, a tertiary alcohol would be at the top of the list.

Based on the Young model, as disclosed in Young 89, a person of ordinary skill in the art would have reasonably expected the compounds of claims 1 and 7 of the '473 patent to be active as LTD_4 antagonists. Tr. 118:16-23, Lenz, Feb. 24, 2009, A.M. session. Young 89 is therefore highly material because it supported a *prima facie* obviousness rejection of claims 1 and 7 of the '473 patent – the

[5] Similarly, Dr. Labelle's testimony that Merck tried many groups before trying the tertiary alcohol is not to the contrary. As Dr. Labelle explained, Merck's testing was based on internal data that suggested that the degree of polarity could play an important role in the Q^2 group. *See* Tr. 16:17-17:6, Labelle, Feb. 23, 2009, P.M. session. But the Young model, as disclosed in Young 89, did not disclose this detail to a person of ordinary skill. Tr. 99:20-22, Young, Feb. 23, 2009, A.M. session; Tr. 118:16-23, Lenz, Feb. 24, 2009, A.M. session. Such a person would act based upon the public disclosure, not based upon Merck's internal data.

structure of the compounds claimed in the '473 patent would have been obvious under the standards applied by the PTO during prosecution.[6]

C. *The Court Should Find that Lopez Withheld the Young 89 Paper with an Intent to Deceive the PTO.*

This Court should find that Mr. Lopez was aware of Young 89, and the Young model, during the prosecution that resulted in the '473 patent, and intentionally withheld the reference from the PTO. Merck, and Mr. Lopez, have offered no explanation, based on any contemporaneous evidence, for the failure to provide Young 89 to the PTO after the examiner focused the prosecution on the distinction between the primary alcohol (in the prior art) and the tertiary alcohol (in the broad pending claims). Instead, Merck asks the Court to infer that Mr. Lopez's failure was a mere oversight, because he cannot recall, today, anything about a decision not to disclose Young 89 during the patent prosecution. Tr. 60:1-6, Lopez, Feb. 24, 2009, A.M. session. While Mr. Lopez offered a general denial that he would ever intentionally withhold material information from the PTO, *id.* at 63:22-25, such a speculative assertion, with no supporting facts or memory, is legally insufficient to explain away as innocent the failure to disclose a highly material paper written by the head of Merck's leukotriene antagonist program. Based upon the facts as established at trial, this Court should conclude that Mr.

[6] Notably, on the first day of trial, Merck implicitly acknowledged the vulnerability of claims 1 and 7 when it dismissed its infringement contentions with respect to claims 1 and 7 *with prejudice*.

Lopez intentionally withheld Young 89, and the Young model it discloses, to deceive the PTO and obtain allowance of the patent.

Mr. Lopez's admissions demonstrate he *was* aware of Young 89, and the Young model, during the patent prosecution. Mr. Lopez admitted that "at the time [he was] prosecuting the 473 patent" he knew "that there was a receptor model" at Merck. Tr. 43:3-10, Lopez, Feb. 24, 2009, A.M. session. Moreover, although he could not recall most details of the model today, he did remember (consistent with the disclosure of Young 89) that Merck's LTD_4 antagonist model had three points of contact with the receptor. *Id.* at 43:23-44:11. And, in the course of his work, Mr. Lopez acknowledged that he would have discussed these issues with Merck's scientists: "I'm sure I must have had a discussion of that sort with people at Frosst, but I don't remember ever having discussed it." *Id.* at 44:11-13. And there is no dispute that Mr. Lopez did, in fact, review and approve for publication the Young 89 article, including the Young model it disclosed. DTX-1410; Tr. 22:4-23:2, Lopez, Feb. 24, 2009, A.M. session.

Mr. Lopez's review of other papers that repeatedly reminded him of the model, and the fact that it had been published in the prior art, further support the conclusion that Mr. Lopez's conduct was intentional. As part of his job, Mr. Lopez was tasked with reviewing manuscripts for publication that were associated with the patent portfolio he was charged with prosecuting. *Id.* at 10:22-12:9. As

the patent prosecutor assigned to deal with the respiratory docket, Mr. Lopez was responsible for many of the patent applications generated by Merck Frosst in Canada, including the LTD_4 antagonist applications. *Id.* at 7:11-23. Mr. Lopez was therefore assigned to review publications concerning LTD_4 antagonists. From November 1987 to April 1992, Mr. Lopez reviewed at least *ten different manuscripts* that referenced or disclosed the Young model. *See id.* at 12:18-41:21; DTX-1207, 1411, 1410, 1285, 104, 105, 1467, 1263, 1465, 1227. The review of these manuscripts began before the applications that resulted in the '473 patent were filed, and continued through the drafting, filing and prosecution. *See, e.g.*, Tr. 38:37:20-38:3, Lopez, Feb. 24, 2009, A.M. session. The last produced review form signed by Mr. Lopez is dated *just one week* before Merck received its second rejection over prior art disclosing a primary alcohol in the Q^2 position, and just four months before Mr. Lopez responded to another such rejection by claiming that the secondary or tertiary alcohol would not be obvious over a primary alcohol. *Compare* Stipulated Fact, at p. 11, ¶ 81 (reciting rejection mailed on April 8, 1992) *and* DTX-1444, at 1444.607-09 (Lopez response dated August 26, 1992) *with* DTX-1227 (Lopez signature on manuscript review form on April 1, 1992). These manuscripts reviewed and approved by Mr. Lopez repeatedly disclosed (1) the existence of the model; (2) the details of the model; (3) the importance of the model to Merck's actual development of LTD_4 antagonists; and (4) that the model

was prior art to the pending application.[7] This timing makes implausible and unreasonable Merck's requested inference that that Mr. Lopez did not recall the model when addressing the Examiner's rejections during the prosecution that resulted in the '473 patent.

At trial, Mr. Lopez tried to minimize any suggestion that he could have learned of the Young model from reviewing these publications. For example, when confronted with a manuscript referencing the Young model which he reviewed on March 22, 1991 (*i.e.*, during the prosecution), Mr. Lopez speculated that he "would have given very little review" to DTX-1465[8] because "the author has already said that there's nothing in here that hasn't already been – not published, but approved for publication." Tr. 39:21-24, Lopez, Feb 24, 2009, A.M. session. Mr. Lopez's speculation continued that the identity of the author, Dr. Young, reinforced this view: "I mean, I didn't go back – ***I'm sure I did not go***

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[7] At the very least, these manuscripts should have put Mr. Lopez on notice that material prior art existed. The Manual of Patent Examining Procedure ("MPEP") specifically provided that Lopez had an obligation to investigate Merck's files for material prior art. *See also* DTX-361. And any claim by the scientists that they believed the legal department would identify relevant prior art, *see* Tr. 110:5-17, Young, Feb. 23, 2009, A.M. session, is legally insufficient to explain the failure to disclose Young 89.

[8] Not only was DTX-1465 reviewed during the prosecution of the '473 patent, it also contained one of the clearest statements of the importance of the model: "In spite of its simplicity, this receptor model has proved very useful in the design and discovery of MK-571, one of the most potent LTD_4 antagonists known to date." DTX-1465, at MSD02396712, 21, 30.

back and verify that statement because the author is representing, and not only the author, but you know, Bob Young was fairly high up in the Frosst research group so that -- . . . I had no reason to doubt that it had already been published – not published necessarily, but cleared for publication." *Id.* at 40:7-14 (emphasis added); *see also id.* at 60:16-61:3 (repeating that he would have taken Young's statements "at face value"). But Mr. Lopez's own contemporaneous handwritten note on a similar document belies his speculative explanation on the stand. Contrary to his claim that he would not have verified Dr. Young's statement that a manuscript contained material that had already been cleared for publication, Mr. Lopez ***did*** investigate Dr. Young's claim that the material in another Young manuscript, Young 89, had been previously cleared. DTX-1410, the manuscript review form for Young 89, contains a notation (like DTX-1465) that "The author has indicated that all of the material in this manuscript was previously cleared in 87-ms-1290." Here, however, Mr. Lopez did not take Dr. Young's representation at face value. Rather, Mr. Lopez acknowledged that he then wrote, "NO – 1290 was an abstract only." DTX-1410 at MSD02113350; Tr. 70:11-22, Lopez, Feb. 24, 2009, A.M. session. The contemporaneous evidence thus confirms, contrary to Mr. Lopez's speculation on the stand, that Mr. Lopez carefully reviewed the manuscripts, including those in which Dr. Young indicated the material had been previously approved for publication.

Not only was Lopez aware of Young 89 and its receptor model, but he also knew or should have known of the high materiality of this information. Mr. Lopez had extensive experience in chemistry and in prosecuting pharmaceutical patents. Mr. Lopez has a Bachelor of Science in Chemistry, for which he took at least five to seven different chemistry courses. Tr. 5:3-11, Lopez, Feb. 24, 2009, A.M. session. By 1990, he had been a patent prosecutor for nearly fifteen years, and had drafted or prosecuted hundreds of patent applications. Tr. 52:1-3, Lopez, Feb. 24, 2009, A.M. session. For nearly his entire career, Mr. Lopez prosecuted patents in the pharmaceutical, or related, fields. *Id.* at 6:2-7:7. And he prosecuted numerous patents as part of Merck's leukotriene antagonist program; over 30 patents have issued related to leukotriene antagonists that, on their face, identify Mr. Lopez as the prosecutor and by 1990, he was spending between 30 and 50% of his time working on patents related to leukotriene antagonists. *Id.* at 8:8-10:15. Mr. Lopez understood that these manuscript reviews were part of his job responsibilities at Merck. *Id.* at 29:12-14. He was assigned to review these manuscripts precisely because they were relevant to patent applications he was prosecuting. *Id.* at 12:5-12:9. And Lopez reviewed the manuscripts in sufficient detail to make editorial comments. *See, e.g., id.* at 17:12-19. Dr. Young similarly vouched for Mr. Lopez's technical acumen, testifying that he had worked with Mr. Lopez on a number of occasions, and always found him to be competent and to understand the

technology. Tr. 111:8-16, Young, Feb. 23, 2009, A.M. session. Mr. Lopez's claim that he did not read or understand the Young model any more carefully than punctuation on the page is inconsistent with Mr. Lopez's education and experience. *See* Tr. 27:6:16, Lopez, Feb. 24, 2009, A.M. session ("Well, yeah, I saw the periods on the page, too, you know, because it was part of the page, but it doesn't mean I read the periods or I read the model. It was on the page."). Mr. Lopez thus must have known, during prosecution, that Young 89, and the receptor model it disclosed, was highly material and yet he did not disclose it. Any suggestion by Merck that Mr. Lopez did not understand the importance of Young 89, and the model it disclosed, is unsupported by the record at trial.

Mr. Lopez also understood his duty of candor to the PTO. He understood, since becoming a member of the Patent Bar in 1976, that he owed a duty of candor to the PTO. *Id.* at 51:21-25. Mr. Lopez understood that this duty of candor required him to disclose material information during prosecution. *Id.* at 52:4-7. And he understood that "material information" was defined as "information that a reasonable examiner would want to know about in evaluating patentability." *Id.* at 52:10-14. In the context of the patent prosecution at issue here, Mr. Lopez testified that, during the prosecution, he was "representing to the examiner here that it would not be obvious to put a secondary or tertiary alcohol at the Q^2 position of the

409 patent." *Id.* at 54:2-7. And that his duty of candor therefore required disclosing any information material to that representation. *Id.* at 54:20-22.

Finally, by 1992, Mr. Lopez was well aware of the importance of the patent that would eventually issue as the '473 patent. He generally attended review meetings about the status of the leukotriene antagonist project, and gave presentations on the status of patent applications. *See, e.g.*, DTX-1533; Tr. 116:7-16, Young, Feb. 23, 2009, A.M. session. In or around July 1991, Lopez also provided Dr. Young (the head of the project) the patent status for L-706,631, *i.e.*, montelukast. PTX-3167, at 3167.0114; Stipulated Fact, at p. 9, ¶ 68. And it was important, both to Dr. Young (the head of the project) and Merck itself that potential commercial products be covered by issued patents. Tr. 117:3-10, Young, Feb. 23, 2009, A.M. session.

In light of these admitted and acknowledged facts, this Court should conclude that Mr. Lopez was aware of (1) Young 89, and the Young model it disclosed; (2) the importance of the Young model, especially in the context of the examiner's rejection over the primary alcohol prior art; and (3) his duty to disclose such important information to the examiner. As Mr. Lopez, and Merck, have offered no explanation for the failure to disclose this highly material reference, the Court should conclude that Lopez withheld the reference with an intent to deceive the PTO and hold the '473 patent unenforceable.

II. Claims 18-22 of the '473 are Obvious.

On the first day of trial, Merck stipulated to the dismissal of its claim of infringement of claims 1 and 7 of the '473 patent *with prejudice*. Thus, the only question of obviousness remaining for the Court is that of claims 18-22 of the '473 patent, which claim montelukast, particular salts, and using the drug. As Dr. Lenz explained at trial, Merck's own extensive prior art publications, including Young 89 in view of the '882 patent and the EP '093, render these claims obvious when one applies standard medicinal chemistry tools. Tr. 125:22-126:5, Lenz, Feb. 23, 2009, A.M. session.

A. *The Level Of Skill In The Art At The Relevant Time.*

Obviousness is determined from the point of view of a hypothetical person whom the law presumes has knowledge of all prior art references in the field of the invention in the relevant time frame – a person of ordinary skill in the art ("POSA"). As claims 18-22 are entitled to a priority date no earlier than August 8, 1991, the relevant time frame for the obviousness inquiry is 1990 to 1991. Stipulated Fact, at p. 13, ¶ 107.

A person of ordinary skill in the art in 1990 to 1991 would be a Ph.D. medicinal chemist or an organic chemist with a minimum of two years of experience in drug discovery, design, development and an understanding of biological assays. The person would not necessarily have experience working with

leukotriene antagonists to begin with but would have brought themselves up to speed before commencing work. *See* Tr. 86:3-19, Lenz, Feb. 24, 2009, A.M. session. Just like any medicinal chemist with general drug development experience, Dr. Lenz brought himself up to speed in the leukotriene area by reviewing the prior art, including literature, patents and patent publications. *Id.* at 86:16-88:3.

B. *Extensive Prior Art Disclosed LTD_4 Antagonists.*

1. The General Approach of a Medicinal Chemist.

In the absence of x-ray crystal structures, medicinal chemists have certain tools available to help them design antagonists. First, a medicinal chemist identifies a structure to work with, starting with either the natural ligand, a known antagonist, or random screening. Tr. 93:23-95:1, Lenz, Feb. 24, 2009, A.M. session; Tr. 50:3-11, 50:22-51:2, 52:6-16, 53:12-54:3, 64:13-65:18 Young, Feb. 23, 2009, A.M. session. Then, a medicinal chemist will mentally parse the molecule into various components and make changes one by one to see what happens. From the modifications of the compounds, a medicinal chemist will develop a "structure activity relationship" or SAR. Tr. 97:15-99:3, Lenz, Feb. 24, 2009, A.M. session. Merck followed this basic procedure in its LTD_4 antagonist program. Tr. 91:1-11, Young, Feb. 23, 2009, A.M. session.

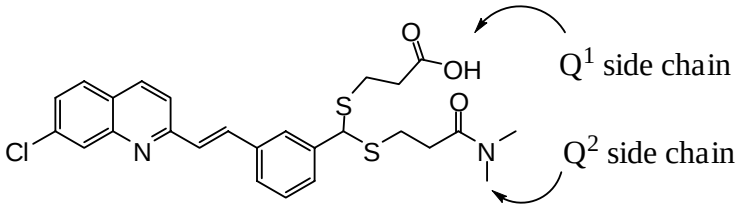
Dr. Lenz identified three "tools" used by medicinal chemists in developing new compounds – (1) ADME, (2) freedom to operate and (3) simplicity. Tr. 95:2-97:14, 98:15-24, Lenz, Feb. 24, 2009, A.M. session. Once again, Merck's witnesses confirmed that Merck used these tools. Tr. 51:3-52:6, 117:6-10, 64:13-65:18, Young, Feb. 23, 2009, A.M. session; Tr. 53:4-13, Labelle, Feb. 23, 2009, P.M. session.

2. Merck Disclosed Much of its Research on LTD_4 Antagonists in the Prior Art.

The prior art included many of Merck's prior compounds. Merck disclosed the Young model in Young 89 (PTX-3283). The Young model taught that the antagonist should possess specific binding qualities in three different portions of the molecule: (1) a lipophilic portion, (2) a hydrophilic portion with ionic bonding and (3) a location where the substituent is polar, not ionized and a hydrogen bond acceptor. Tr. 115:22-117:10, Lenz, Feb. 24, 2009, A.M. session. Moreover, the lipophilic portion of the molecule should have extended conjugation and co-planarity. *Id.* at 126:19-23.

Young 89 disclosed that Merck used the Young model to develop L-660,711, one of the most potent LTD_4 antagonists known at the time, and it generally taught what attributes were required to get an LTD_4 antagonist. *Id.* at 119:15-22, 118:16-23. Young 89 taught that the dimethyl amide portion of L-660,711 binds in the pocket labeled B on the Young model, the polar, non-ionized,

hydrogen bonding site, while the acid portion of L-660,711 binds to the other polar pocket. *See* Tr. 118:4-10, Young, Feb. 23, 2009, A.M. session; 12:15-17, Gleason, Feb. 25, 2009, P.M. session; Tr. 26:11-16, Lenz, Feb. 24, 2009, P.M. session; *see also* 12:18-23, Gleason, Feb. 25, 2009, P.M. session. Young 89 is prior art to claims 18-22 of the '473 patent. Stipulated Fact, at p. 14, ¶ 113.



L-660,711

Merck further disclosed and patented the enantiomers of L-660,711[9] in the '409 patent which issued on July 25, 1989, Stipulated Fact, at p. 15, ¶ 128; Tr. 10:8-11:3, Gleason, Feb. 25, 2009, P.M. session; 105:4-5, Lenz, Feb. 24, 2009, A.M. session. According to the '409 patent, the acid chain of L-660,711 is the Q^1 side chain and the dimethyl amide chain of L-660,711 is at the Q^2 side chain. *See* Tr. 11:68-12:14, Gleason, Feb. 25, 2009, P.M. session. The '409 patent is prior art to claims 18-22 of the '473 patent.

Merck's development, as disclosed in the prior art, did not stop at L-660,711 but rather continued with other quinoline compounds. Merck went on to disclose and patent their next generation compounds in EP '093 and the '882 patent. Tr.

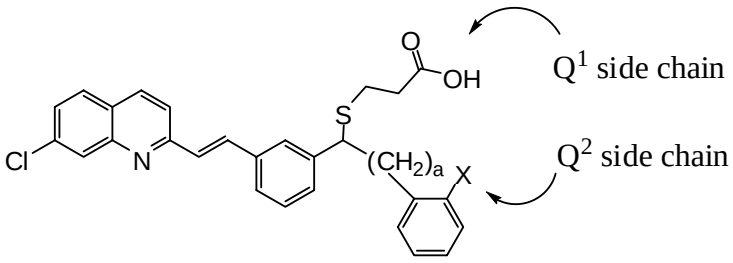
[9] Verlukast is one of the enantiomers of L-660,711. Tr. 17:1-2, Lenz, Feb. 24, 2009, P.M. session.

104:25-105:8, Lenz, Feb. 24, 2009, A.M. session. EP '093 was published on May 31, 1989 (Stipulated Fact, at p. 15, ¶ 125) and is therefore § 102(b) prior art to claims 18-22 of the '473 patent. Merck's '882 patent issued on April 14, 1992 from application serial no. 527,236, which was filed on May 22, 1990. Stipulated Fact, at p. 15, ¶ 132. The '882 patent is § 102(e) prior art to claims 18-22 of the '473 patent.

C. *The Asserted Claims Of The '473 Patent Are Obvious Over Young 89 In Combination With Merck's '882 Patent And EP '093*

1. The Disclosure Of Young 89 And The '882 Patent Would Lead A Person Of Ordinary Skill In The Art To A Lead Structure.

Based on a review of Young 89, the '882 patent and EP '093, a medicinal chemist attempting to find additional leukotriene antagonists would work with the following lead structure:

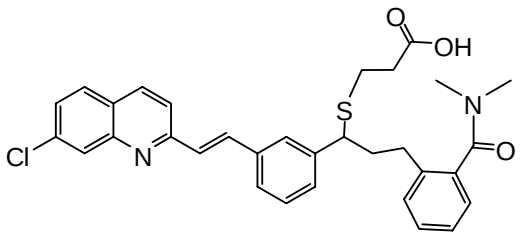


Lead Structure

Tr. 126:1-23, Lenz, Feb. 24, 2009, A.M. session. This lead structure incorporates the three structural attributes identified as necessary for an LTD_4 antagonist by Young 89. *Id.* at 126:11-127:14; 127:23-128:20. But a POSA would not stop with Young 89; recognizing that the development of LTD_4 antagonists was a fast

moving research field, a POSA would use the most up-to-date prior art available and therefore would look to changes made by Merck in the '882 patent and EP '093. *Id*. at 127:14-23. These prior art references suggest adding a phenyl ring on the Q^2 side chain,[10] resulting in a lead structure that is consistent with the Young model. Tr. 126:6-128:20, Lenz, Feb. 24, 2009, A.M. session. According to the Corey experiments referred to in Young 89, the Q^1 and Q^2 side chain of the lead structure is not interchangeable in the binding pockets of the receptor. In other words, Q^1 is the acid side chain and Q^2 would be the side chain containing the amide. Tr. 19:8-11, 20:24-21:1, 24:10-13, Lenz, Feb. 24, 2009, P.M. session; Tr. 31:20-32:3, Lenz, Feb. 25, 2009, A.M. session.

Of the compounds disclosed in the '882 patent, a POSA would have chosen Compound 97 as a particularly preferred compound.



Compound 97

[10] The removal of the sulfur from the Q^2 side chain is also consistent with the state of the art at the time. A POSA would understand that Merck first copied the two-sulfur side chains from SK&F. Tr. 66:22-67:5, Young, Feb. 23, 2009, A.M. session. By 1990/91, SK&F had dropped one of the sulfurs. Tr. 16:9-19:7, Gleason, Feb. 25, 2009, P.M. session. A POSA would have understood that just like SK&F, Merck dropped one of the sulfurs from one of the polar side chains in its next generation compounds. Tr. 19:8-20:9, Gleason, Feb. 25, 2009, P.M. session.

Compound 97 is the compound where "X" is a dimethyl amide, the substitution L-660,711 shows has superior properties. Tr. 128:21-129:9, Lenz, Feb. 24, 2009, A.M. session.

2. A Person Of Ordinary Skill In The Art Would Modify Compound 97 to Montelukast.

A POSA looking to develop leukotriene antagonists would not modify the quinoline ring and the phenyl ring linked by a double bond because the entire portion is the extended conjugation taught by Young 89. Tr. 129:14-16, Lenz, Feb. 24, 2009, A.M. session; Tr. 14:4-16:8, Gleason, Feb. 25, 2009, P.M. session. Instead, a POSA would modify the polar chains, Q^1 and Q^2. A POSA would homologate the Q^1 chain by adding a methylene group (CH_2). Homologation is standard operating procedure for a medicinal chemist.[11] Tr. 129:17-25, Lenz, Feb. 24, 2009, A.M. session. Indeed, in making modifications to a compound in Merck's LTD_4 antagonist project, Dr. Labelle modified the compound by varying the chain length. Tr. 26:21-23, Labelle, Feb. 23, 2009, P.M. session.

[11] The prior art reference Perchonock (PTX-3143) disclosed three carbon homologs. Perchonock confirms that making homologs is a standard medicinal chemistry operation. The two carbon chain and three carbon chain analog in Perchonock had the same biological activity. Tr. 22:17-22, 23:19-25:10, Lenz, Feb. 25, 2009, A.M. session.

A POSA would also understand that fatty acid chains, such as the Q^1 chain, are subject to beta-oxidation.[12] To prevent beta-oxidation, a medicinal chemist would put either two methyl groups or a cyclopropyl group in the beta position. Tr. 130:1-131:13, Lenz, Feb. 24, 2009, A.M. session. Inventor Leger noted that one metabolic issue he was dealing with, with respect to the side chain, was oxidation. He admitted that the first approach in trying to prevent the oxidation of the side chains was to add substitution to the side chain. Leger Dep. 84:14-85:7, May 14, 2008.

After making these modifications to the Q^1 side chain, a POSA would turn to the Q^2 side chain. A POSA would modify the Q^2 side chain by substituting the dimethyl amide with a polar, non-ionized, hydrogen bond acceptor, the critical attributes identified by Young 89. Of the possible groups to put on the Q^2 side chain, a tertiary alcohol would be one of the first groups a medicinal chemist would use. Tr. 131:14-132:14, Lenz, Feb. 24, 2009, A.M. session. Dr. Labelle agreed that the tertiary alcohol was a likely modification – "a logical step" – given

[12] At trial, Merck suggested that a paper by Newton would suggest that beta oxidation would *not* occur in compounds of this structure. PTX-3141. While the compounds disclosed in Newton are chemically similar to the lead structure, they differ significantly metabolically because of the long hydrocarbon chain subject to omega oxidation. Tr. 11:10-13, 12:6-10, 25:18-27:8, Lenz, Feb. 25, 2009, A.M. session.

what was known at the time. Tr. 60:6-61:15, Labelle, Feb. 23, 2009, P.M. session.[13]

Finally, a POSA would recognize that the compound resulting from the modifications outlined above would be a racemate, a mixture of enantiomers. The prior art directed a POSA to separate the racemate into the enantiomers. Tr. 105:19-106:2, 132:15-133:1, Lenz, Feb. 24, 2009, A.M. session. The resulting compound is the compound of claim 18 of the '473 patent, montelukast. *Id.* at 125:18-25, 133:2-8. A POSA would reasonably expect montelukast to be biologically active. *Id.* at 133:2-8. Claim 18, montelukast, is therefore obvious. Claim 19-22 are similarly obvious, as they claim simply the sodium salt of montelukast (claim 19); a pharmaceutical composition using montelukast (claim 20); and using montelukast as a leukotriene antagonist (claim 21) or to treat asthma (claim 22). *See id.* at 133:15-135:1.

[13] At trial, Merck implied that a paper by Ku would suggest that an alcohol would *not* be a good substitution. A person of ordinary skill in the art would not have been able to make any realistic structure-activity relationship conclusions from Ku (PTX-3139). Ku was published in 1985. By 1990, the field has progressed dramatically. The Ku compounds are 6,000 to 28,000 times weaker than L-660,711. By the relevant timeframe, all Ku would tell someone of skill in the art was that an alcohol would be consistent with activity. Tr. 65:5-8, 66:4-17; 67:13-15, Lenz, Feb. 24, 2009, P.M. session; Tr. 20:13-17, 21:9-22:16, Lenz, Feb. 25, 2009, A.M. session.

D. *Plaintiff's Evidence Of Secondary Considerations Cannot Overcome the Structural Obviousness of Montelukast.*

To conclude there is a nexus between the invention and secondary considerations of nonobviousness, the Court must consider whether the claimed compound provides superior asthma or allergy relief, the indications for which leukotriene antagonists are directed. Montelukast sodium is the active ingredient in the products sold by Merck under the tradename Singulair®. Stipulated Fact, at p. 9, ¶ 68. Because Singulair® does not, in fact, provide superior asthma or allergy relief, Plaintiff cannot demonstrate that the claimed invention solves an unmet need, provides unexpected results or that commercial sales are attributable to the invention itself.

1. Singulair® Does Not Provide Superior Asthma Relief.

Inhaled steroids are the "gold standard" for asthma treatment. Tr. 24:18-23, Barnes, Feb. 4, 2009. Asthma guidelines recommend beginning treatment with inhaled steroids, which are safe and effective. DTX-3017; Tr. 13:21-14:8, 61:23-62:7, 63:13-64:24, Barnes, Feb. 4, 2009; Tr. 72:24-73:11, Meltzer, Feb. 25, 2009, P.M. session. Inhaled steroids are very well tolerated and are very easy to take for both children and adults. Tr. 28:6-29:24, Barnes, Feb. 4, 2009. Singulair® is not even the first choice as an add-on therapy to inhaled steroids. Rather, the preferred approach is to include an inhaled long acting beta-agonist as an add-on therapy. *Id.* at 24:18-25:8.

Singulair® is less effective than inhaled steroids as an initial controller of asthma. *Id.* at 32:21-22, 65:9-24. The NAEPP guidelines conclude that studies demonstrate that inhaled steroids improve asthma control in both children and adults more effectively than anti-leukotrienes or any other single long-term control medication. *Id.* at 61:23-62:7, 64:15-24. Indeed, Dr. Barnes reported that he has taken patients off of Singulair® and, not a single patient reported their asthma getting worse as a result of discontinuing Singulair®. Nor did he have a patient request to be placed back on Singulair®. *Id.* at 40:22-42:7. Merck, itself, recognized the efficacy problem with montelukast. An internal Merck presentation (DTX-331) noted that after three months, approximately 60% of patients stopped using Singulair®, with 80% of the patients discontinuing Singulair® treatment after a year. Tr. 98:22-99:8, Jaffe, Feb. 23, 2009, P.M. session; Williams Dep. 180:7-20, July 9, 2008. More patients (31%) discontinued treatment with Singulair® than for any other asthma medication because "[i]t was not effective/didn't work well enough." DTX-331. Singulair® thus does not answer any unaddressed need for new asthma therapies that was present in 1990 to 1991 or even today. Tr. 8:23-9:7, 68:15-69:12, Barnes, Feb. 4, 2009.

2. Singulair® Does Not Provide Superior Relief For Allergic Rhinitis.

Nor does Singulair® provide superior relief for allergic rhinitis. The preferred treatment for allergic rhinitis is topical steroids, either as a nasal spray or

nasal drops. If steroids are insufficient, then a second generation anti-histamine is included in the treatment. Tr. 36:3-9, Barnes, Feb. 4, 2009. While Singulair® has some efficacy in treating allergic rhinitis, all of the studies have shown that it is less efficacious than nasal steroids and antihistamines. Tr. 67:7-20, Barnes, Feb. 4, 2009; Tr. 77:2-14, Meltzer, Feb. 25, 2009, P.M. session.

3. Merck's Extensive Promotion of Singulair® Contributed To Its Alleged Commercial Success.

Merck recognized that it needed to promote Singulair® to generate additional prescriptions. Tr. 98:12-100:16, Jaffe, Feb. 23, 2009, P.M. session.[14] Merck's advertising and promotional activities significantly contributed to the sales of Singulair®. *Id.* at 73:21-74:2, 112:4-12. From 1998 to 2007, Merck's annual total promotional spending increased from $**REDACTED** to $**REDACTED**. *See* PTX-3262, at Exhibit 8-B. In the ten years Singulair® has been sold commercially, Merck has spent more than $**REDACTED** on two broad categories of activities of marketing and promotion: (1) promotional activities aimed at consumers; and (2)

[14] *See also*, DTX-235, at p. 9: "Singulair continues to suffer from low efficacy perceptions, and is not considered a first or second choice when selecting an agent on efficacy." Physicians surveyed did not consider Singulair® to be best in class from an efficacy standpoint. Tr. 15:17-17:3, Vellturo, Feb. 26, 2009, A.M. session. DTX-235, at p. 30, reports that only 18% of physicians surveyed said that Singulair® provides effective asthma control. Considerations for Singulair® were based on other attributes of the drug. Tr. 17:4-18:9, Vellturo, Feb. 26, 2009, A.M. session.

activities aimed at doctors. Tr. 74:22-76:8, Jaffe, Feb. 23, 2009, P.M. session; PTX-3262, at Exhibit 8-B.

At trial, Merck argued that its promotional advertising to consumers and doctors provided nothing more than information on the benefits of Singulair®. Tr. 106:10-12, 106:25-108:14, Vellturo, Feb. 25, 2009, P.M. session. Yet, Dr. Vellturo is not an expert in marketing or in promotional messaging. Tr. 107:23-25; Jaffe, Feb. 23, 2009, P.M. session; Tr. 12:15-18, 13:3-4, Vellturo, Feb. 26, 2009, A.M. session. He has no special training or experience that qualifies him to determine whether a promotional message accurately and fairly communicates content. Tr. 13:21-24, Vellturo, Feb. 26, 2009, A.M. session. Nor does he have any training to evaluate the psychological aspects of the Singulair® advertisements that he reviewed. *Id.* at 12:19-13:2; 13:5-12. Dr. Vellturo's cursory review of Merck's direct-to-consumer advertising involved review of storyboards of television advertisements for Singulair® and not the actual television commercials for Singulair®. *Id.* at 11:8-12:5.[15]

Merck's position, presented by Dr. Vellturo, is belied by Merck's internal documents. The majority of Merck's marketing and promotional activities aimed at consumers, direct to consumer advertising ("DTC advertising"), consisted of

[15] In reaching his conclusions, Dr. Vellturo also did not consider Merck's other extensive patent portfolio, which serves as a barrier to entry and prevents other companies from attempting to commercialize products similar to montelukast. Tr. 109:7-110:2, Jaffe, Feb. 23, 2009, P.M. session.

television ads. Merck's DTC advertising was crucial to the sales of Singulair®. Tr. 76:12-77:3, Jaffe, Feb. 23, 2009, P.M. session. Merck's internal documents quantifying the economic effect of DTC advertising on sales (DTX-705, DTX-706, DTX-1475) acknowledge that DTC advertising accounted for a substantial portion of the sales of Singulair®, (Tr. 77:16-83:24, Jaffe, Feb. 23, 2009, P.M. session), as Dr. Vellturo conceded. Tr. 91:1-18, Jaffe, Feb. 23, 2009, P.M. session. Similarly, Merck's internal documents show that Merck's promotional activities caused physicians to prescribe more Singulair®. Tr. 93:10-16, Jaffe, Feb. 23, 2009, P.M. session. In fact, Merck recognized that physicians do not distinguish among products based on their rational attributes. Rather, it is the emotional attributes that distinguish products. Emotional attributes are defined by the distinct personality, unique branding and breakthrough promotional imagery associated with Singulair®. *Id.* at 111:14-112:3; DTX-137. Merck thus acknowledged, contrary to Dr. Vellturo's assumptions, that it is *not* the information about the efficacy of a drug that results in successful promotion and sales.

CONCLUSION

The evidence at trial establishes that Merck obtained the '473 patent through inequitable conduct, by intentionally withholding the highly material Young 89 reference. Moreover, the evidence established that the only remaining claims in

the case, claims 18-22 of the '473 patent, are invalid as obvious over Merck's own prior art publications. The Court should accordingly rule in favor of Defendants.

Dated: March 18, 2009

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